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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,296	05/25/2001	Eugene A. Woltering	98M06.1 Woltering	4311
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PATENT DEPARTMENT TAYLOR, PORTER, BROOKS & PHILLIPS, L.L.P P.O. BOX 2471 BATON ROUGE, LA 70821-2471			EXAMINER AFREMOVA, VERA	
			ART UNIT 1651	PAPER NUMBER

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

95

Office Action Summary

Application No.

09/866,296

Applicant(s)

WOLTERING ET AL.

Examiner

Vera Afremova

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10,13,38 and 39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-10,13,38 and 39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☒ Interview Summary (PTO-413) Paper No(s). 10/07/2003.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

Status of claims

Claims 1-10, 38 and 39 as amended [10/17/2003] are pending and under examination in the instant office action.

Claims 11, 12, 40 and 41 were canceled by applicants [10/17/2003]. Claims 14-37 were canceled by applicants [2/03/2003].

Information Disclosure Statement

Upon applicants' request the information disclosure statement with respect to the "other information" has been acknowledged. However, 2 preprint documents that are submitted as manuscripts and indicated on the PTO-1449 form, are not publications. Thus, in the absence of proper citations they are not considered within the meaning of 37 CFR 1.98 (b)(5).

Response to Arguments

Applicants' arguments and amendments [10/17/2003] have been fully considered.

Some of the applicants' arguments [10/17/2003] have been found persuasive with respect to the pending claims as amended.

The claim rejections under 35 U.S.C. 102(b) as being anticipated by Brown et al. or Montesano et al. or US 5,976,782 have been withdrawn because that methods of the cited references encompass applications of general angiogenesis models based on culturing isolated blood vessels and/or tissues that are not 3D tumor samples as encompassed by the presently claimed invention. The claim rejection under 35 U.S.C. 102(b) as being anticipated by Lugassy et al. has been withdrawn because the method of cited reference encompasses the use of a tumor that is rebuilt in an *in vitro* system from the separated cell suspensions and that is not an original

Art Unit: 1651

3D tumor biopsy sample with intact architecture as encompassed by the presently claimed method. Thus, claim rejection under 35 U.S.C. 103(a) as being unpatentable over Montesano et al. taken with Brown et al., Lugassy et al., US 5,976,782 and US 5,856,184 has been withdrawn because the cited prior art combined neither teaches nor fairly suggests the presently claimed method.

Some of the applicant's arguments with respect to claims as amended have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

Claims 1-5, 7, 8, 10, 13, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of assaying angiogenic potential of a three-dimensional tumor embedded in fibrin matrix, does not reasonably provide enablement for enabling for method of assaying angiogenic potential of a three-dimensional tumor embedded in collagen-containing matrix. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Nature of the invention is drawn to a method of assaying angiogenic potential of a three-dimensional tissue sample embedded into a matrix (page 1, par. 3).

Breadth of the claims is drawn to a method of assaying angiogenic potential of a three-dimensional tumor sample embedded into a matrix.

Amount of guidance and working examples are drawn to the use of a fibrin matrix for assaying angiogenic potential of a three-dimensional tumor sample (page 25, par. 2).

Art Unit: 1651

State of the prior art demonstrates that the use of the collagen material-containing matrix did not allow for practicing method of assaying angiogenic potential of a three-dimensional tumor sample (tumor biopsies) due to rapid degradation of the matrix and outgrowth of the cells of tumor biopsies in the matrix. For example: see reference by Barendsz-Janson et al. {Journal of Vascular Research. 1998, 35:109-114} at page 111, col. 2, lines 3-15. The reference states that the model with the tumor biopsies and the collagen material-containing matrix is not reliable and not reproducible. Thus, the state of the art demonstrates unpredictability of the model system for assaying angiogenic potential as encompassed by the presently claimed invention. Claims 8 and 10 are also included in the instant rejection because gelatin is derived from collagen and Matrigel contains collagen materials. Therefore, neither specification nor the prior art can be said to support the enablement of the claims over their breath.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

As set forth in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. *Ex parte Humphreys*, 24 USPQ2d, 1260.

Art Unit: 1651

Thus, the scope of the claims is not commensurate with the teachings of enablement of the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2-6, 13, 38 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Gulec et al. [Journal of Surgical Research. 97:131-137. May 15, 2001. IDS reference].

Claims are directed to a method for assaying angiogenic potential of a particular tumor in a mammal wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the growth of angiogenic vessels as a measure of the angiogenic potential wherein in the method the tissue sample is taken from a particular tumor in a mammal, wherein the tissue sample comprises blood vessels and multiple cell layers but not isolated artery or vein and wherein the tissue sample has intact architecture. Some claims are further drawn to the use of medium with or without serum, to the use of medium supplemented with various factors including vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) for observing differences in angiogenesis in various systems. Some claims are further drawn to the use of matrix such as fibrin or others. Some claims are further drawn to

Art Unit: 1651

additional steps of monitoring control tumor tissue samples with factors affecting or inhibiting angiogenesis.

The reference by Gulec et al. discloses a method for assaying angiogenic potential of a particular tumor in a mammal as a measure of the growth of angiogenic vessels. In the method of the cited reference the tissue sample is harvested or taken from a particular tumor in a mammal (page 113, col.1, par. 2), the tissue sample of tumor xenograft is a biopsy sample and it has been created in mice by injecting particular tumor cells and, thus, it is a particular tumor that comprises blood vessels and multiple cell layers but not isolated artery or vein and has intact architecture (page 134, col. 1 par. 1-3) within the meaning of the instant claims. The method of the cited reference comprises step of embedding 3D tumor sample in fibrinogen (page 134, col. 1, par. 5), step of supplying the embedded tumor sample with a medium (page 134, col. 1 par. 4-6), step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the growth of angiogenic vessels (page 134, col. 2, par. 2 and table 1). The disclosed culture media is serum-free and comprises endothelial growth factors derived from EGM (endothelial growth medium). The method comprises additional steps of monitoring control tumor tissue samples with factors affecting angiogenesis such as somastotin analogs (page 134, col.1, last par.).

Thus, the cited reference teaches identical structural elements are identical active steps as required by the presently claimed method.

Claim Rejections - 35 USC § 103

Art Unit: 1651

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2-6, 9, 13, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulec et al. [May 15, 2001; IDS reference] taken with US 5,616,478.

Claims 1, 2-6, 13, 38 and 39 as explained above. Some claims are further drawn to the use of various matrix materials including agar, agarose, alginate or silica gel in the method for method for assaying angiogenic potential of a particular tumor in a mammal.

The reference by Gulec et al. is relied upon as explained above. The cited reference is lacking particular disclosure related to the use of various matrix materials for assaying tumor related angiogenesis. However, US 5,616,478 teaches the use of various organic and inorganic substances including agar or agarose, silica gel and alginate that are used in biotechnology as support or as matrices for growing and immobilizing biological materials including animal cells (col. 7, lines 14-21).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the method for assaying angiogenesis by using various organic and inorganic substances or matrices including agar or agarose, silica gel and with a reasonable expectation of success in assaying growth and physiological response of animal cells including tumor cells or samples because the presently claimed matrix materials have been known the prior art as suitable materials for growing and studying various biological materials including animal cells. Thus, one of skill in the art would have been motivated to use

Art Unit: 1651

various matrix materials suitable for biological samples and for studying physiological responses for the expected benefits in identifying therapeutically active substances which affect, enhance or suppress animal cells including tumor cells. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351 till January 15, 2004 or (571) 271-0914 after January 15, 2004. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743 till January 15, 2004 or on (571) 272-0926 after January 15, 2004.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova



AU 1651

VERA AFREMOVA

January 9, 2004

PATENT EXAMINER